# Swelife-SDP4

# Gene Therapy

## Manufacturing of Gene Therapy Products: A Swedish Perspective

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# Introduction

## Background

This work is part of the Vinnova-financed Swelife-ATMP system development project SDP4 Gene therapy. The project aims to identify opportunities and challenges for Sweden to become internationally leading in the field of gene therapy, building upon literature studies and discussions with stakeholders in industry and academia. This report presents findings and reflections and describes the current initiatives, capabilities and needs related to production of gene therapy products in Sweden.

The current report builds upon the work "Pilot Study of a Swedish Institute for Cell Therapy" conducted by RISE Research Institutes of Sweden, financed by Vinnova and presented in a report in 2018. The chapter on gene therapy described commercial potential, global challenges, weaknesses and advantages in Sweden and proposed short- and long-term activities within the field. Overviews that monitor ongoing projects were suggested in order to enable new collaborations, and to encourage and collect suggestions on initiatives that strengthen public financing for the field of gene therapy. This report target both parts.

## Aim

The aim of this report is to increase the understanding of what infrastructures for manufacturing of gene therapy products (pre-clinical and clinical) that exist in Sweden today, and what infrastructure that is needed from an industry point of view for the scale up of the production of gene therapy products to meet future demands. It covers strategic platforms, research centers, contract research and manufacturing organizations (CRO/CMO) and other core functions that support upscaling of gene therapy production.

The report offers an overview that can function as a base for discussions on national strategic activities in the field, and for companies that evaluate their prospects in translating products under development into commercial gene therapy products.

## Methodology

The report is based primarily on interviews and discussions with national stakeholders from academia and industry, including companies that offer equipment, materials and other services to parties that develop gene therapy

products. Information has also been collected from databases, scientific literature and stakeholder websites.

## Current state of gene therapy development

Therapeutic products that falls into the category of Advanced Therapy Medicinal Products (ATMP) include gene therapy, cell therapy and tissue engineered products. Gene therapy refers to techniques that modify patient genes in order to treat a disease and has been the focus area for this work.

The product type and mechanism of action of gene therapy products varies, and several subclassifications exists. It is practical to distinguish between virus-based and non-viral systems. The most common virus-types used for transfection are adeno-, adeno associated (AAV), lenti- and retro-viruses[1]. Non-viral systems include a wide variety of solutions such as liposomes, various functionalized and bare polymer particles, as well as the use of naked plasmid DNA or RNA.

The classification of ATMP's sometimes bridges several types. One example is the increasingly popular CAR-T technology (chimeric antigen receptor T cell), in which T cells from a patient are gene modified *ex vivo*, expanded and then reinjected into the patient as a cell therapy. This report only covers *in vivo* gene therapy strategies.

The most suitable infrastructure for manufacturing of ATMP's varies depending on the product type; products with a large demand and sufficient stability are suitable for central manufacturing, while unstable products for a small patient population may be better to produce in-house where it was developed. This has been described in a recent scientific publication, in which some considerations for choosing a manufacturing strategy are highlighted.[2] An intermediate solution is presented in the article, suggesting centralized logistics (consumables, staff training, management of equipment and quality) and local manufacturing of the final product.

In general, a facility that produces certain viral vectors should be able to produce other types of viral systems. However, practical experience with the

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[1] http://www.abedia.com/wiley/index.html, the Gene Therapy Clinical Trials Worldwide database provided by the Journal of Gene Medicine (Wiley). Cited: 17 October 2019.
[2] Special Topic Commentary: A. Bak, K. P. Friis, Y. Wu and R. J. Y. Ho, "Translating Cell and Gene Biopharmaceutical Products for Health and Market Impact. Product Scaling From Clinical to Marketplace: Lessons Learned and Future Outook." Journal of Pharmaceutical Sciences 108 (2019) 3169-3175.

specific vector system increases the success rate markedly. This applies especially to the downstream processing of the products (i.e. purification and quality control analyses), where adaptations are needed for every new type of viral vector. The available equipment at a CMO is an important factor since any change in the process may have negative impact on the outcome. Thus, it is a major point of consideration for a company that searches for a CMO for their production what vector systems they are already working with, which limits the options.

## Internationally

Companies that need CRO/CMO services for gene therapy products search internationally to find the most suitable facilities and competence. Most CMO's in Europe are experienced in production of adenovirus and lentivirus. An important aspect to consider is that materials that are produced using biological systems are sensitive for environmental differences. Thus, a close and continuous contact between the concept owner and the CMO is crucial for successful manufacturing, and this benefits from geographical proximity.

An example of a large strategic investment in Europe that connects research and industry is the British Catapult platforms, of which one branch is a center focusing on gene and cell therapy[3]. It consists of a development center and a manufacturing center that support both researchers and companies. The investment by the government is substantial but has led the Cell and Gene Therapy Catapult to become ahead of most corresponding CRO/CMO's in Europe. Meanwhile, because of the collaborations with CRO/CMO's, the investment value spreads. For example, the international manufacturing company Cobra Biologics that has facilities in Sweden has collaborated with and gained knowledge through Catapult.

During the interviews, some other international hubs have also been mentioned as successful. In Copenhagen, the system supports a mixture of small, medium-sized and large companies to co-exist. The National Institute for Bioprocessing Research and Training, NIBRT[4], in Ireland offers for example GMP courses for industrial clients and research on biopharmaceutical manufacturing and has beneficial establishment systems that has promoted investments in manufacturing sites in the area.

[3] https://ct.catapult.org.uk/, Cell and Gene Therapy Catapult (UK). Cited: 24 October 2019.
[4] https://www.nibrt.ie/, National Institute for Bioprocessing Research and Training (IRL). Cited: 15 November 2019.

## In Sweden

There are many gene therapy initiatives in Sweden and the majority is focusing on research or strategical perspectives. The product development of viral vector-based therapies in Sweden is driven mainly by companies, according to the sources used for this report, and only a few academic groups focus on this. Only 13 clinical trials with gene therapy products had been conducted in Sweden as by 2017,[1] although current initiatives aim at delivering more gene therapy products to the Swedish market. The general viewpoint of involved parties is that the field holds a great potential and that it is important to connect various development activities.

It has been raised in discussions that the relatively low number of academic driving forces and CMO options in Sweden might be an obstacle for small and medium-sized enterprises (SME's) that aim to drive the development of gene therapies all the way to a commercial product, since sensitive product systems need specific competence and experience, together with well-functioning dialogues, as discussed above.

There is a functional infrastructure for plasmid production in Sweden (described in the next chapter) but less options for virus production at large scale. For viral vectors, companies must look outside Sweden to find suitable CMO's with capacity to deliver GMP material, although they would prefer a Swedish CMO. In addition to research projects directly focusing on gene therapy development, the expertise in mammalian cell lines as production hosts is high in Sweden and could be one of the key strengths for further development in the ATMP area.

Non-viral gene therapy systems, like liposomes, can often be produced in less specialized laboratories. It may be easier to scale-up the production of some of the virus- and cell free delivery vehicles if the systems are less sensitive for change in conditions or environments than other ATMP types. Sweden has strong academic expertise on non-viral gene delivery systems (e.g. through the current research node FoRmulaEx) and some Swedish SME's are also active in this area. This niche could be a strength to build upon with relatively modest investments.

Large pharmaceutical companies have the possibility and ambition to invest in their own production sites to cover market demands. A suggestion is to instead focus the discussions on common infrastructure investments on SME needs, which is the main perspective covered by this report.

# Gene therapy activities in Sweden

Several organizations are currently active in gene therapy development. The largest efforts are listed in Table 1. Here, they are divided into the categories: research, translation, retail or production, according to their major focus.

Table 1. Organizations and initiatives active in gene therapy process development in Sweden.

| *Organization* | *Location/ coordination* | *Time* | *Category* | *Capabilities* | *Target product* |
|---|---|---|---|---|---|
| ***FoRmulaEx*** | *Chalmers, Gbg* | *2017-2022* | *Industrial research centre (SSF)* | *Development of drug-delivery vehicles for nucleotide drugs and analytical tools* | *RNA* |
| ***AdBIOPRO*** | *KTH, Sthlm* | *2017-2022* | *Competence centre (Vinnova)* | *Development of continuous production processes* | *Viral vectors and cell products* |
| ***CAMP*** | *Umeå University* | *2018-2023* | *Competence centre (Vinnova)* | *Development of bioprocesses, infrastructure and logistics* | *All ATMPs* |
| ***Pre-GMP facility*** | *Karolinska Institutet, Sthlm* | *From 2020* | *Translation, infrastructure* | *Pilot production, validation runs, SOP development* | *Plasmids, viruses, cell therapy, tissue therapy* |
| ***Vecura*** | *Karolinska University Hospital, Sthlm* | | *Translation, infrastructure* | *Final process development and GMP production* | *Primarily cell therapy. 0.1 - 1 g plasmid.* |
| ***GE Healthcare*** | *GE HC Uppsala* | *n.a.* | *Retail* | *Equipment and materials needed for scale-up and production of cultivations and purifications* | *Cells, plasmids and viral vectors* |
| ***Cobra Biologics*** | *Matfors* | *From 2019* | *Production, CMO* | *Batch size for plasmid production: 50 L in use, 500 L being built.* | *Plasmids, 4-40 g* |

## Research

Public funding agencies have during recent years supported the foundation of several research and competence centers focusing on gene and cell therapies with partners from both academia and industry. FoRmulaEx and AdBIOPRO started in the same year and are coordinated at Chalmers and KTH, respectively. FoRmulaEx, the industrial research center for functional RNA delivery, work primarily with nucleotide drugs, developing non-viral vehicles and analytical tools for gene therapy evaluation. Encapsulation and delivery mechanisms are major interests. AdBIOPRO, center for advanced bioproduc-

tion, focuses on bioproduction by continuous processing and target both cell products and viral vectors. CAMP, center for advanced medical products, is a research center that targets the translations from lab to clinic and also connects academic and industrial partners.

## Translation

There are several medium sized enterprises in Sweden that offer contract research and manufacturing of biological products, although few are experienced in gene therapy products. Two of the largest infrastructures for translational development and pilot production of ATMP's are the pre-GMP facility at Karolinska Institutet, and Vecura at Karolinska University Hospital. Vecura is an established GMP qualified production environment that can produce ATMP for clinical studies. However, practical experience within gene therapy is less than within cell therapy and the high occupancy makes it challenging to support early stage process development. This is a motivation behind the construction of the pre-GMP facility that is currently starting up their activities at Karolinska Institutet. Their aim is to facilitate the early process development activities for translation from lab-scale to large-scale production in an environment resembling GMP.

## Production

Among cell-free gene therapies, the current production sites in Sweden has the highest availability and experience in plasmid production. Liposome based gene therapies are still mainly found in the research phase. Virus production is more common for vaccines than as gene therapy products, and there is no current large-scale production site for that available in Sweden. Some interest exists among manufacturing organizations, although restricted by the small and uncertain customer base.

Vecura, mentioned above, supports production of ATMP for clinical studies. Retroviruses have been produced there earlier, although few gene therapy projects have been run during the last years partly due to higher demands on availability for cell products. More hands-on experience for gene therapy products would be beneficial.

Cobra Biologics is an international CRO/CMO with large facilities in Matfors in Sweden. They have recently invested in a large-scale production unit for high quality (HQ) and GMP quality plasmids. When completed, 500 L cultivations are possible, for yields of 40 g plasmid. This is one of the largest batch capacities for plasmid production in Europe.

## Availability and identified requirements from case studies

CMO's are available outside Sweden and is a viable option for a Swedish company that needs to start producing material. This may however lead to fewer biopharma industry activities in Sweden. It has been raised during the interviews that it is the small companies that are affected the most by the lack or presence of development and production infrastructures and CMO's within the country since they have restricted economy and lack in-house infrastructure.

Plasmid production is available in Sweden via Cobra Biologics. Coordination between Vecura and Cobra Biologics is ongoing to harmonize plasmid production from pre-GMP to GMP within one of the Vinnova funded competence centers, CAMP. The initiative will help researchers and small companies to access small quantities of HQ plasmid DNA for toxicity studies and/or virus production. Moreover, coordination of production together with Cobra Biologics will ensure that at least one commercial vendor will have capacity for production of larger quantities of GMP-material required for clinical studies.

The development of single-use bioreactors is positive since it facilitates scale-up as well as enables the production unit to be more flexible with the variety in the processes that will be needed when working with different types of biopharmaceuticals.

Among the opinions expressed in the collection of input for this report is that the risks will stay too high in the translation from development phase to commercial product without independent support, which in turn discourage venture capitalists to support/invest in the activities. A local initiative similar to Catapult has been suggested during interviews to hold potential as encouragement for more companies to engage in the area because of the reduced risk of forcing to stop between a research grade product and commercial product.

There are different opinions about whether Sweden should invest in an infrastructure similar to Catapult or not. Alternatives that have been suggested include increased support for 1) collaboration between academic groups, 2) existing clean room facilities in hospitals, and 3) CMO's that has own R&D interests. The CMO's can then support SME's with expertise within production requirements and with starting material. A concept similar to SciLifeLab (or expansion of it) has also been suggested, functioning as a hub

that includes relevant service centers and connects also with educational programs.

In parallel, certain other aspects must be discussed and given support, such as adapted regulatory routes.

The issue has been raised that available education have insufficient coverage of GMP and other necessary competence, which hampers the expansion of CMO's. Competence for product and process development within the field of ATMP is largely taken care of by research centers and within industry R&D. However, this results in mostly research and strategic expertise and do not necessarily increase the availability of competence for production sites. Likewise, when an academic group or start-up company turns to a facility for process development and production, availability of personnel with industrial experience is considered valuable.

The key findings from interviews with actors in different stages of the development phase, with main focus on SME perspectives, are presented in the illustration below (Figure 1). Both infrastructural sites and relevant competence in ATMP production and GMP has been raised as needs.

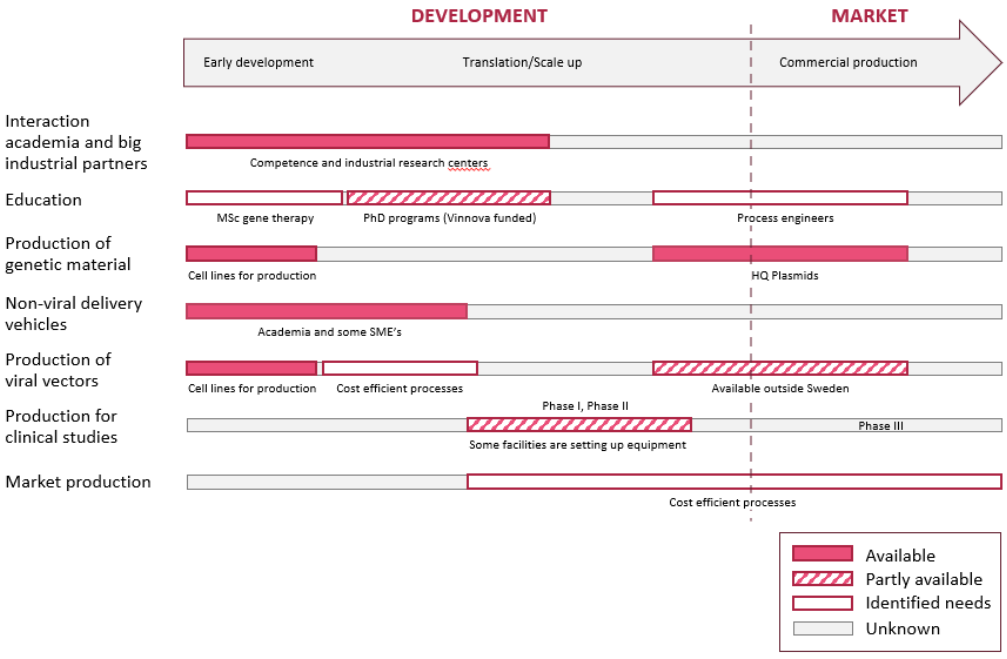


Figure 1. Illustrative overview of key findings showing areas that are fully or partly accessible, and identified gaps and needs, with focus on academia and SME's.

As support for further discussion, the topics discussed herein that are suggested to be of most importance have been sorted into a SWOT matrix to highlight strengths, weaknesses, opportunities and threats (Figure 2).

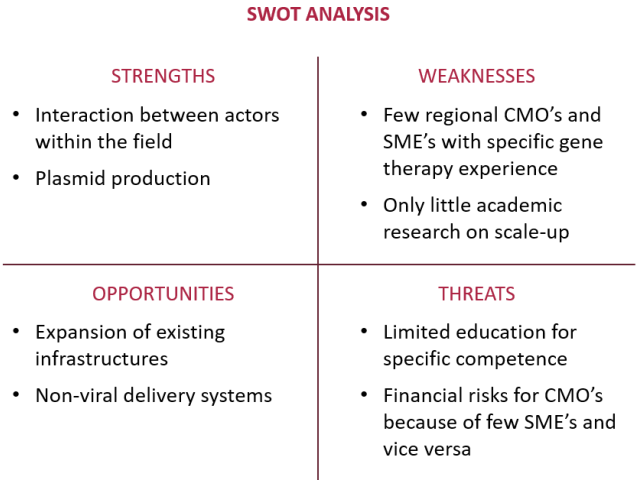


Figure 2. SWOT matrix that highlights topics covered by this report that are suggested as a base for further discussions.

It is relevant to consider what type of financial support that cost-efficiently utilizes opportunities and weaknesses so that the threats are diminished; for example how to ensure relevant competence supply and a supportive environment for SME's and CMO's.

## Suggestions for discussion forums

This report has compiled the viewpoints of various actors within the field of gene therapy development in Sweden. In order to make meaningful conclusions, the comments and viewpoints needs to be considered in relation to each other and discussed with actors from various types of organizations to identify areas of priorities. We encourage workshops around different scenarios. The following topics can be used as starting points for such discussions.

- If Sweden would make a huge investment for something similar to Catapult, what would be the expected and realistic outcome? Would the cost be motivated by that outcome? Who would benefit the most? Is there a risk that some types of organization get outrivalled?
- What is the expected scenario if no big national investment is made?

- Are there other options that could support specific parts of the process chain that could be more cost-efficient?
- How can we ensure competence within the gene therapy area? What are the most important measures to take?
- What is needed to take products from Phase II production to Phase III in clinical studies and does that process need external support?
- Are there certain niches that Sweden could/should focus on?
- Does the illustration (Figure 1) match the current situation?

# Other actors

Attached is a list of more actors working with related topics that could add valuable comments in future discussions.

| *Organization* | *Relevance for gene therapy* | |
|---|---|---|
| ***Vironova*** | *Virus analysis* | *https://www.vironova.com/application-areas/gene-therapy-vaccine/* |
| ***Novartis*** | *Development of novel ATMP's* | *https://www.novartis.com/our-focus/cell-and-gene-therapy/key-focus-areas* |
| ***Uppsala therapeutics*** | *Development of novel ATMP's* | *https://uppsalatherapeutics.com/* |
| ***OxThera*** | *Development of novel ATMP's* | *http://www.oxthera.com/about-us/* |
| ***Camurus*** | *Development of novel ATMP's* | *https://www.camurus.com/camurus* |
| ***Biovian*** | *CMO for viral vectors in Finland* | *http://www.biovian.com/about_us* |
| ***APL*** | *Aseptical production facilities* | *https://www.apl.se* |
| ***Recipharm*** | *Aseptical formulation and manufacturing* | *https://www.recipharm.com* |
| ***Galenica*** | *CRO/CMO for clinical use* | *https://galenica.se* |
| ***Adlego*** | *CRO/pre-GMP, part of the CAMP centre* | *https://adlego.se* |

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## List of contributing parties

This report is based on discussions with the following participants:

| | |
|---|---|
| CombiGene | Karin Agerman |
| Cobra Biologics | Eva-Karin Gidlund, Ola Tuvesson |
| Vecura | Pontus Blomberg |
| SumIT system | Anders Hagman |
| Scandinavian Development Services | Andrea Salmén |
| FoRmulaEx | Erik Nilebäck |
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